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EXAMINER	
GOLDBERG, JEANINE ANNE	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/567,074	SCHERER ET AL.	
	Examiner	Art Unit	
	JEANINE A. GOLDBERG	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26,34-39 and 41-48* is/are pending in the application.

4a) Of the above claim(s) *1-3, 6-25, 34-39, 42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,5,26,41 and 43-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed March 5, 2009. Currently, claims 1-26, 34-39, 41-48 are pending. Claims 1-3, 6-25, 34-39, 42 have been withdrawn as drawn to non-elected subject matter.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.

3. Any objections and rejections not reiterated below are hereby withdrawn.

Maintained Rejections

Election/Restrictions

4. Applicant's election with traverse of Group II, Claims 4-5, 26, 31, 41, 43-46 in the paper filed June 30, 2008 is acknowledged.

The examiner thanks applicants for pointing out that Claims 43-46 were inadvertently grouped with Group I when they should be grouped with elected Group II. Claims 43-46 are hereby placed in Group II.

Moreover, Claim 31 which depends on Claim 31 is within Group II.

The response further asserts that restriction to a single polymorphism is unduly restrictive. The response asserts that there would not be a serious search and examination burden to the Office and request reconsideration of the restriction requirement to include at least all of the variants to the EMP2B gene identified in the specification. This argument has been reviewed, but is deemed not persuasive. Current Claim 4 appears to be drawn to a generic linking claim. In the event that an

allowable generic linking claims is found, the examiner will consider rejoinder of the variants encompassed within the scope of the allowable generic linking claim. However, no allowable generic or linking claim has been presented at this time.

Applicants argue that they are entitled to claim the entire genus of variations of the EPM2B gene that are associated with Lafora's disease. The response states that the members of the genus have a substantial common structure, namely the nucleic acid sequence of EPM2B, as set forth in SEQ ID NO: 1. This argument has been reviewed but is not persuasive. The "substantial common core" is known in the art, namely the "wild type" EPM2B gene is known in the art. It is the differences between the common core that applicants (i.e. the variants) are relying upon for patentability and not the common core structure that was known in the art. Thus, the variants are drawn to what is different from the common core and not the commonality of the core.

Claims 1-3, 6-25, 31, 34-39, 42 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement.

The requirement is still deemed proper and is therefore made FINAL.

This application contains claims 1-3, 6-25, 31, 34-39, 42 have drawn to an invention nonelected with traverse in the paper filed June 30, 2008. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Priority

5. This application is a 371 of PCT/CA04/01449, July 30, 2004 which claims priority to 60/491,968, filed August 4, 2003.

Information Disclosure Statement

6. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

a. The specification contains a list on pages 56-60 of the specification.

Claim Objections

7. Claim 48 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 47 requires analyzing a nucleic acid test sample for SEQ ID NO: 1. The claim does not permit any alternative sequence. However, Claim 48 is directed to variations of SEQ ID NO: 1. Thus, Claim 48 fails to limit Claim 47 because Claim 48 does not appear to be within the scope of Claim 47.

8. Claim 48 refers to table 1. MPEP 2173.05(s) states:

Where possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. Incorporation by reference is a necessity doctrine, not for applicant's convenience."

Appropriate correction is required.

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 4, 41, 45 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims broadly encompass any mutation which is a missense, nonsense, insertion, deletion, point mutation or frameshift which "affects a portion of the EPM2B gene encoding a RING finger domain or an NHL motif of SEQ ID NO: 1".

Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from

its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA…' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. With respect to claims which encompass variants, as provided in Example 7 of the Written Description Guidelines, no common structural attributes identify the members of the genus. The current claims encompass a large genus of nucleic acids which comprise missense, nonsense, insertion, deletion, point mutation or frameshift which "affects a portion of the EPM2B gene encoding a RING finger domain or an NHL motif of SEQ ID NO: 1". The genus includes an enormous number of mutations for which no written description is provided in the specification. The specification teaches 21 particularly named mutations (see page 55). Only 12 of these mutations are within the RING or NHL motifs of the EPM2B gene. The art teaches that additional mutations have been found (see Ianzano et al. Human Mutation

Database in Brief #847, http://projects.tcag.ca/lafora). In the database, of mutations of NHLRC1 (EPM2B), 51 mutations have been indexed. The database classifies several missense mutations as mutations and not associated with disease. Moreover, Lohi et al. (Neurology, Vol. 68, pages 996-1001, 2007) teaches hidden and novel Lafora disease gene mutations and likely coding mutations. The Table notes that several of the mutations cause protein truncations or no protein is made, but 7 mutations are not taught to cause any deleterious effect on the encoded protein (see page 1000).

According to Table 1, the following mutations appear to be within the scope of the newly amended Claims.

RING	NHL1	NHL2	NHL3	NHL4	NHL5	HNL6
C26S	D146N		Q226X	E279K	G321fs2	
F33S			V16fs1	Q29P	E340fs40	
P69A				S298fs15		
P69fs21						

It is noted that the specification fails to provide any mutations within NHL2 or NHL6. Furthermore, only one mutation is within NHL1. The art teaches a diagram of mutations and their location within the gene (see Singh et al. (J. Med. vol. 43, 2006). The diagram places at least 2 additional mutations in NHL1. Moreover, Singh teaches mutations in both NHL2 and NHL6. At the time the invention was made, the 12 mutations within the scope of the claims was not representative of the mutations claimed.

The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, mutations of SEQ ID NO: 1 which in the RING and NHL motifs of SEQ ID NO: 1 alone is insufficient to describe the genus. There is no description of the mutational sites that exist in nature and there is no description of how the structure of SEQ ID NO: 1, namely EPM2B/NHLRC1, relates to the structure of any mutations. The general knowledge in the art concerning mutations does not provide any indication of how the structure of one allele is representative of unknown alleles. The nature of alleles is such that they are variant structures, and in the present state of the art the structure of one does not provide guidance to the structure of others. The common attributes are not described. The specification provides no correlation between structure of mutations and the function of such mutations. The mutations shown are not representative of the genus of any mutation associated with Lafora's disease because it is not clear which mutations within the gene (coding or non-coding) region of Lafora nucleic acid would have the same effect. One of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of only one member of this genus is not representative of the variants of the genus and is insufficient to support the claim. Accordingly, Applicants have not adequately disclosed the relevant identifying characteristics of a representative number of species within the claimed genus.

Response to Arguments

The response traverses the rejection. The response asserts the claims have been amended to be directed to mutations that affects a portion of the EPM2B gene encoding a RING finger domain or an NHL motif and wherein the mutation is associated with the presence of Lafora's disease. This argument has been considered but is not convincing because, as discussed above, the disclosure of 12 mutations within the claimed regions is not representative of all the mutations within the scope of the claims. The claims do not appear to encompass any mutations within the NHL2 or 6 motif regions. Moreover, it is unclear whether the mutation must merely be within the regions claimed or whether there has to be some "affect" on the portion of the gene. In the event the later is required, applicant has not described what affect is required and which mutations have such an affect.

The response argues that the specification provides 21 examples of mutations that fall within the scope of the genus. This argument has been reviewed but is not convincing. While the Table comprises 21 mutations, it is noted that not all these mutations are within the RING finger domain or NHL motifs. Only 12 of the mutations appear to be within the claimed regions. And as noted previously, there are no mutations within two of the NHL motifs provided.

Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

> art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 4-5, 26, 41, 43-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

A method of detecting Lafora's disease in a human subject comprising obtaining a sample from the human subject and

detecting a G at position 205 of SEQ ID NO: 1

wherein the presence of a G at position 205 of SEQ ID NO: 1 is indicative of Lafora's disease,

does not reasonably provide enablement for a method of detecting Lafora's disease by detecting a missense, nonsense, insertion, deletion, point mutation or frameshift which "affects a portion of the EPM2B gene encoding a RING finger domain or an NHL motif of SEQ ID NO: 1". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

11. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 4-5, 26, 31, 45 are drawn to a method of detecting Lafora's disease by detecting a missense, nonsense, insertion, deletion, point mutation or frameshift which "affects a portion of the EPM2B gene encoding a RING finger domain or an NHL motif of SEQ ID NO: 1".

Claim 41 is drawn to a method of detecting the presence of Lafora's disease in a human comprising detecting a mutation in the EPM2B gene nucleic acid sequence wherein the mutation "affects a portion of the EPM2B gene encoding a RING finger domain or an NHL motif of SEQ ID NO: 1".

Claim 43 is drawn to a method of detecting the presence or absence of a mutation in the EPM2B gene by comparing the test sample to a nucleic acid sequence set forth in SEQ ID NO: 1 and determining the differences. The claim broadly encompasses any test sample.

Claims 44, 46 are drawn to a method for diagnosing the presence or predisposition to Lafora's disease by analyzing a nucleic acid sample from a human to determine the presence of a EPM2B gene mutation listed in Table 1 wherein the presence of an EPM2B gene mutation indicates the individual has or is at risk for development of Lafora's disease.

Claims 47-48 are directed to detecting SEQ ID NO: 1 and sequences with mutations of Table 1.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The art teaches genetic mapping of a new Lafora progressive myoclonus epilepsy locus (EPM2B) on 6p22. Chan et al. (J. Med. Genet. Vol. 40, pages 671-675, 2003) states they have identified a second LD gene locus named EPM2B at 6q22 based on a study of LD families from a F-C isolated. Chan teaches a nine marker haplotype is identical and homozygous in all patients (page 874, col. 1).

Chan et al. (Nature Genetics, Vol. 35, No. 2, pages 125-127, September 2003) teaches mutations in NHLRC1 cause progressive myoclonus epilepsy. NHLRC1 is also called PEM2B. Chan teaches the identification of 17 different DNA sequence alterations in 26 families which were not present in 100 control chromosomes (Page 125, col.2). Table 1 illustrates a summary of mutations associated with Lafora disease. Chan teaches the C205G nucleotide chance is P69A which causes a missense RING finger, however provides no information whether this alteration causes a deleterious effect on the protein product.

Ianzano et al. (Human Mutation database in Brief #847, 2005) teaches Lafora progressive myoclonus epilepsy mutation database-EPM2A and HNLRC1 (EMP2B) genes. The database for Lafora progressive myoclonus epilepsy mutation and polymorphisms is accessible at http://projects.tcag.ca/lafora. On August 22, 2008 the data base was accessed and there are 51 entries for EPM2B/NHLRC1.

Singh et al. (J. Med Genetics, Vol. 43, e48, 2006) teaches novel NHLRC1 mutations and genotype-phenotype correlations in patients with Lafora's progressive myoclonic epilepsy. Singh teaches identification of 5 new mutations. Figure 1 provides a representation of 39 mutations in the NHLRC1 gene and the frequency. P69A appears to be the most frequent mutation found.

Lohi et al. (Neurology, Vol. 68, pages 996-1001, 2007) teaches a heterozygous

deletion of the entire EPM2B gene and seven new mutations. Table 1 illustrates mutations which are missense, but no analysis of the effect on the protein has been provided. Moreover, the table notes one variant as a SNP rather than a mutation.

The level of unpredictability in associating any particular allele with a specific phenotype is even higher. The high level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification. There is a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases. However, the art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state.

Lucentini (The Scientist; 2004, vol 24, page 20) teaches that most gene association studies are typically wrong. Lucentini teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical methods, should be included in the gene association studies (middle column, 1 st complete paragraph). In the instant case, the specification only provides information that the variants within EPM2B exist, but provides no guidance that it has any effect on the EPM2B gene, expression, or activity, let alone any potential diagnostic effect.

The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied

three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

The art teaches that presence of SNPs in the same gene does not indicate that each of the genes is associated with the same diseases. Meyer et al. (PG Pub 2003/0092019), for example, teaches that SNPs in the CADPKL gene are not each associated with neuropsychiatric disorders such as schizophrenia. Specifically Meyer teaches that cadpkl5 and cadpkl6 are not associated with the disease, however cadpkl7 has a p-value of less than 0.05, therefore an association exists. Each of these polymorphisms are SNPs within the CADPKL gene, however, it is apparent that they are not all associated in the same manner with disease. Thus, Meyer exemplifies that the association of a single SNP in a gene does not indicate that all SNPs within the gene are associated with the disease.

Guidance in the Specification.

The specification provides no evidence that all missense, nonsense, or frameshift mutations in SEQ ID NO: 1 cause a deleterious effect on the encoded protein or are associated with Lafora's disease.

The specification teaches 17 different DNA sequence alterations are described in EPM2B in 26 families including 8 deletions and 1 insertion leading to frame-shifts, 7 missense, and 1 non-sense change (Table 1). These mutations were found in families in both homozygous (18) and compound heterozygous (8) recessive states. The most common mutation identified (7 families) was a homozygous 205C.fwdarw.G transition resulting in a proline to alanine change in the RING-finger domain.

All of the mutations detected would affect the putative RING or NHL motifs, or would be predicted to lead to a frame-shift or cause drastic structural change in the protein (LD483 carries a 260T.fwdarw.C nucleotide change which would lead to a leucine to proline alteration).

Four silent DNA sequence-coding variants were identified. Three of them T312C (H104H), G372C (G124G) and T1020C (G340G) were present in five, two, and one of 100 control chromosomes, respectively. The most common polymorphism detected, C332T (P111L) (FIG. 1) was observed on 42 of 100 control chromosomes.

The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to enable the skilled artisan to practice the claimed invention as broadly as claimed.

The claims are broadly drawn to detecting Lafora's disease by detecting Lafora's disease by detecting any missense, nonsense, insertion, deletion, point mutation or frameshift which "affects a portion of the EPM2B gene encoding a RING finger domain or an NHL motif of SEQ ID NO: 1". The claims appear to state that the presence of any missense, nonsense, insertion, deletion, point mutation or frameshift which "affects a portion of the EPM2B gene encoding a RING finger domain or an NHL motif of SEQ ID NO: 1" is indicative of Lafora's disease. This logic does not appear to be supported by the evidence of record. The specification teaches P111L is present in 42/100 control chromosomes. The specification does not appear to analyze the mutations for any significant association. Thus, it is unpredictable which missense, nonsense, insertion, deletion, point mutation or frameshift which "affects a portion of the EPM2B gene encoding a RING finger domain or an NHL motif of SEQ ID NO: 1" are associated with Lafora's disease. At the time the invention was made, the specification taught 17 variations within 26 families. One of these variations was found in a high percentage of control chromosomes. It would have been unpredictable at the time the invention as made to determine and know which variations of SEQ ID NO: 1 are associated with Lafora's disease absent further unpredictable and undue experimentation. While the skilled artisan could assay for additional mutations, it would have been unpredictable which variations are indicative or diagnostic of Lafora's disease.

This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the association of mutations and diseases has not been established it is unpredictable the skilled artisan could practice the claimed invention as broadly as claimed. The prior art and the specification provides insufficient guidance to overcome the art recognized difficulties of association studies. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The response traverses the rejection. The response asserts that the evidence discovered by Applicants demonstrates that mutations in these specific regions of the protein encoded by SEQ ID NO: 1 *are likely* to be associated with Lafora's disease. This argument has been considered but is not convincing because the response sets forth and fails to point to the evidence they are relying upon. The evidence of the record demonstrates that controls and Lafora's patients share the same mutations. Thus, there

is no evidence that there is any significant association between any particular mutation and Lafora's disease. The state of the art at the time the invention was made, as evidenced by Hirschorn, Lucentini and Ioanndis makes clear that association studies require replication and robustness to make assertions.

The response asserts that the claimed invention has been mischaracterized because Claims 26, 44 and 46 are directed to specific mutations. This argument has been reviewed but is deemed not persuasive. Although the particular mutations have been found in families with Lafora disease, this does not suggest that these are mutations which are associated with Lafora disease. The specification, in fact, teaches T312C (H104H), G372C (G124G) and T1020C (G340G) were present in five, two, and one of 100 control chromosomes, respectively. The most common polymorphism detected, C332T (P111L) (FIG. 1) was observed on 42 of 100 control chromosomes. There is no statistically significant analysis that the mutations are indicative of presence or predisposition to Lafora's disease.

With respect to Claim 43, directed to methods of detecting presence or absence of mutations, the word mutation is presumed not to the same as a natural variation. As noted above, the specification has found the variations in control and disease chromosomes suggesting that the variations are not indicative of a mutation.

The response argues that the specification provides at least 17 examples of mutations that are associated with Lafora's disease. This argument has been reviewed but is not convincing. While Table 1 comprises 21 mutations, it is noted that not all these mutations are within the RING finger domain or NHL motifs. Only 12 of the

mutations appear to be within the claimed regions. And as noted previously, there are no mutations within two of the NHL motifs provided. It is further unpredictable that each of these mutations are significantly associated with Lafora's disease since a number of them are also found in control patients.

Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

12. No claims allowable.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is

(571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz, can be reached on (571)272-0763.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

/Jeanine Goldberg/
Primary Examiner
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